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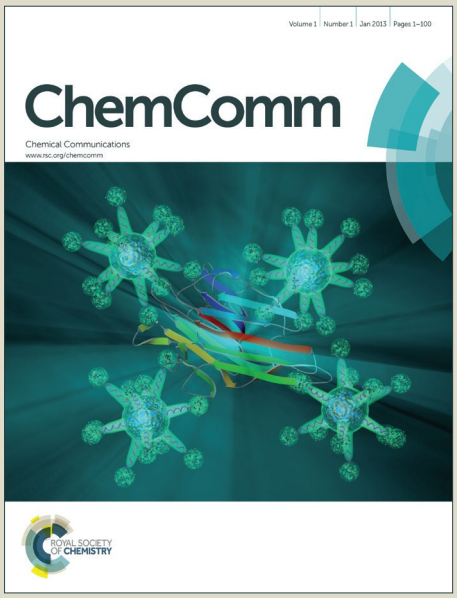

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Copper-catalyzed alkylarylation of activated alkenes using isocyanides as the alkyl source: An efficient radical access to 3,3-dialkylated oxindoles

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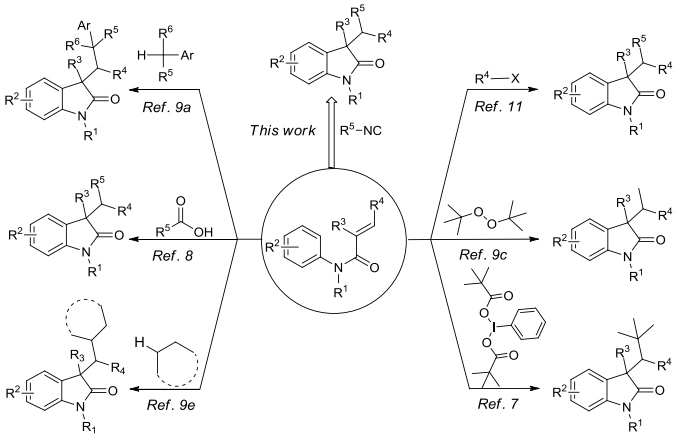
A novel and efficient protocol for the synthesis of 3,3-dialkylated oxindoles is described. The method involves a copper-catalyzed tandem radical addition/cyclization of *N*-arylacrylamides with the alkyl radicals generated from isocyanides. Two C–C bonds are formed in a single step.

3,3-Disubstituted oxindoles are one of the most prominent *N*-containing heterocyclic scaffolds, widely present in bioactive natural products and pharmaceuticals.[1] As a consequence, numerous synthetic strategies have been developed during the past few decades to construct oxindoles.[1a,2] Over the years, free radical chemistry has become an effective tool in organic synthesis and has contributed significantly in the evolution of chemistry. Because of their simplicity and relatively high synthetic efficiency, free radical tandem reactions have been frequently utilized for constructing complex (hetero)polycyclic skeleton.[3] Towards this end, the direct difunctionalization of *N*-arylacrylamides by sequential intermolecular addition of radicals followed by intramolecular cyclization has proven to be an efficient approach to generate 3,3-disubstituted oxindoles.[4,5]

Alkyl groups are one of the most commonly occurring structural features in numerous bioactive natural products and are known to exert significant influence on drug metabolism.[6] Thus, exploring efficient strategies for the incorporation of alkyl groups into bioactive organic molecules, such as oxindoles, is challenging and highly desirable. In the past few years, several elegant works have been reported for the successful incorporation of different alkyl groups into the C3-position of the oxindole scaffold (Scheme 1). In 2012, Liu and co-workers reported an efficient organo-catalytic strategy for the tandem radical addition/cyclization of *N*-arylacrylamides with the *tert*-butyl radical generated *via* the thermal decomposition of bis(pivaloyloxy)iodo]benzene.[7] In 2013, Zhu and co-workers have described a visible-light-promoted access to alkyl radicals from aliphatic carboxylic acids.[8] Similarly, the synthesis of 3-ethyl-3-substituted oxindole derivatives have been reported where di-*tert*-butyl peroxide[9c] or dicumyl peroxide[9d] have been used as methyl radical precursor. Also, (hetero)arylmethanes, phenylethane, and cumene can act as alkyl radical precursors in tandem radical addition/cyclizations with *N*-arylacrylamides under Lewis acidic conditions.[9a] Similarly, toluene[9b] and simple alkanes[9e] have been successfully employed as radical precursors for the efficient synthesis of alkyl-substituted oxindoles under Cu-catalysis. In addition to this, C(sp^3)–H bonds adjacent to the heteroatom have also been employed as radical precursors to access functionalized oxindoles via oxidative alkene 1,2-alkylarylation of *N*-arylacrylamides.[10] In a recent report, Duan and co-workers have utilized unactivated alkyl halides containing a β-hydrogen as alkylating reagents in a palladium-catalyzed difunctionalization of activated alkenes.[11] However, increasing



Scheme 1: Some previous strategies towards 3,3-dialkylated oxindoles.

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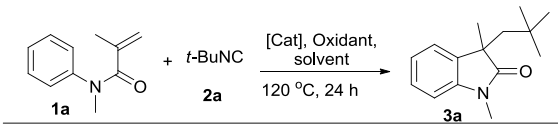
the diversity of the available synthetic methods in this area would be interesting.

Isocyanides are irreplaceable building blocks in organic synthesis[12] and have profound applications in multicomponent reactions[13] and as versatile C1 synthons[14] in transition metal catalysis. It is well known that addition of a free radical initiator to an aliphatic isocyanide leads to the formation of an imidoyl radical species, which undergoes unimolecular β-scission to yield the corresponding alkyl radical. This could be trapped by a suitable reactive moiety.[15] Therefore, we envisaged that the difunctionalization of alkenes with isocyanides through a tandem radical addition/C(sp^2)–H cyclization process could result in a highly interesting approach to oxindoles containing a quaternary carbon center. To the best of our knowledge, the present study is the first report on the employment of isocyanides for the alkylarylation of activated alkenes to incorporate a 3,3-dialkyl moiety into an oxindole scaffold.

First we examined the reaction of *N*-arylacrylamide **1a** (0.1 mmol) and *tert*-butyl-isocyanide **2a** (0.5 mmol) under various reaction conditions (Table 1). Using $CuCl_2$ (15 mol%) as catalyst and DCP (3 equiv) as oxidant in EtOAc at 120 °C for 24 h, the desired product **3a** was obtained in 70% yield (entry 1). Subsequently, the effect of different oxidants (entries 2, 3) and solvents (entries 4, 5) was investigated. However a significant lower yield was observed in each case. Employing organic bases such as Et_3N and DBU as additives failed to afford better results (entries 6, 7). Among the different catalytic systems tested, Cu_2O gave the best result (entries 8-10). Also, CuCl was found effective for the above transformation, albeit providing **3a** in lower yield (entry 8). Further, optimization focused on the molar ratio of the reactants (entries 11, 12), catalyst (entries 13, 14) and oxidant (entry 15). This did not result in an amelioration of the conditions. When the reaction time was reduced to 12 h, a considerable decrease in product yield was observed (entry 16). Without the addition of a Cu-salt a considerably diminished yield was obtained (entry 17). The reaction was also found feasible with iron catalysts but in comparatively lower yield (entries 18-20).

Having optimized the reaction conditions (Table 1, entry 10), we evaluated the scope and limitations with substituted *N*-arylacrylamides. To our satisfaction, the optimized conditions were found to be generally applicable for substituents having different electronic properties on the aromatic ring (**3b**-**3l**). However, a substrate bearing a strong electron-withdrawing group like NO_2 gave an unsatisfactory result (**3k**). In the case of *N*-arylacrylamides bearing a *meta*-substitutent, a mixture of isomers was observed (**3f**, **3g** and **3l**). Also, different alkyl, phenyl or benzyl substituents on nitrogen

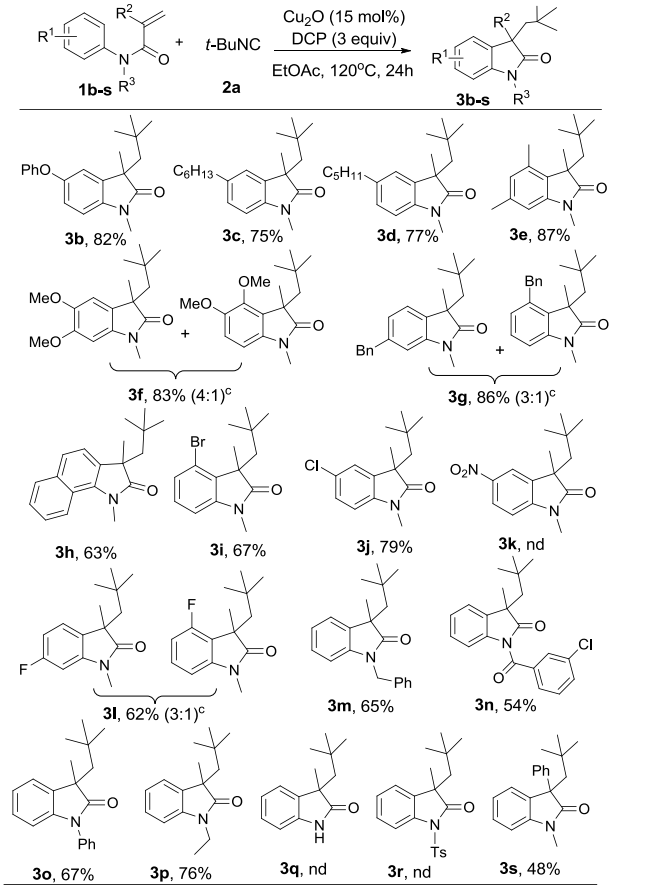
Table 1 Optimization of the reaction conditions.[a]



Entry	Catalyst	Oxidant	Solvent	Yield (%)[b]
1	$CuCl_2$	DCP	EtOAc	78(70)
2	$CuCl_2$	DTBP	EtOAc	26
3	$CuCl_2$	TBHP	EtOAc	nd
4	$CuCl_2$	DCP	$C_2H_5Cl_2$	traces
5	$CuCl_2$	DCP	CH_3CN	38
6[c]	$CuCl_2$	DCP	EtOAc	55
7[d]	$CuCl_2$	DCP	EtOAc	76
8	CuCl	DCP	EtOAc	73
9	$Cu(OAc)_2$	DCP	EtOAc	65(55)
10	**Cu_2O**	**DCP**	**EtOAc**	**83(77)**
11[e]	Cu_2O	DCP	EtOAc	49
12[f]	Cu_2O	DCP	EtOAc	83
13[g]	Cu_2O	DCP	EtOAc	65
14[h]	Cu_2O	DCP	EtOAc	76
15[i]	Cu_2O	DCP	EtOAc	71
16[j]	Cu_2O	DCP	EtOAc	68
17	-	DCP	EtOAc	20
18	$FeCl_3$	DCP	EtOAc	71
19	$FeCl_2$	DCP	EtOAc	73
20	Ferrocene	DCP	EtOAc	56

[a] Conditions: **1a** (0.1 mmol), oxidant (0.3 mmol), catalyst (15 mol%), **2a** (0.5 mmol), solvent (1 mL) at 120 °C for 24 h. [b] NMR yields; isolated yield in parentheses. [c] Et_3N (10 mol%) as additive. [d] DBU (10 mol%) as additive. [e] **2a** (0.3 mmol). [f] **2a** (0.7 mmol). [g] Cu_2O (5 mol%). [h] Cu_2O (10 mol%). [i] DCP (0.2 mmol). [j] reaction time =12 h. DCP = Dicumyl peroxide. DTBP = Di-*tert*-butyl peroxide. TBHP = *tert*-Butyl hydroperoxide.

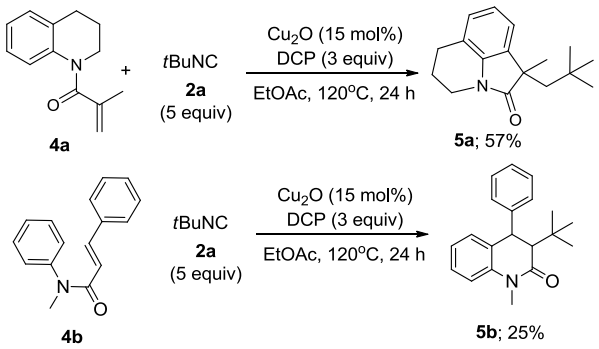
Table 2 Scope of *N*-arylacrylamides.[a, b]



[a] Reaction conditions: **1b-s** (0.2 mmol), **2a** (5 equiv), DCP (3 equiv), Cu_2O (15 mol%), EtOAc (2 mL) at 120 °C for 24 h. [b] Isolated yield. [c] Ratio of isomers determined by ^{1}H-NMR; nd = not detected.

were well tolerated (**3m**-**3p**). On the contrary, a free –NH or electron withdrawing tosyl group was found to be incompatible with these conditions (**3q**, **3r**). It turned out that acrylamide derived from atropic acid (**3s**) gave a relatively low yield, which might be attributed to steric factors.

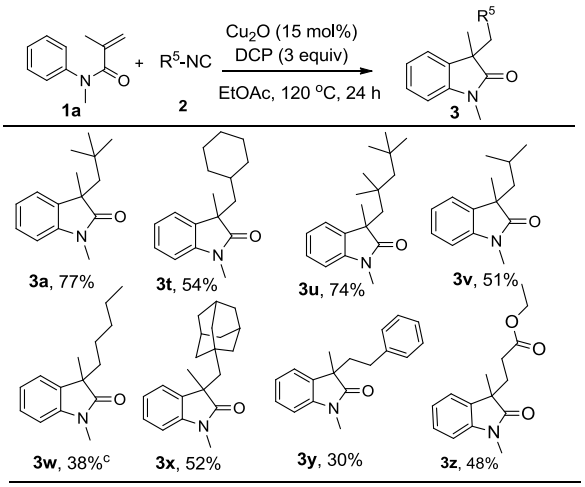
Further, the above protocol was successfully extended to a domino reaction starting from 1-(3,4-dihydroquinolin-1(2*H*)-yl)-2-methylprop-2-en-1-one **4a** (derived from 1,2,3,4-tetrahydroquinoline) delivering compound **5a** in 57% yield (Scheme 2). However, use of cinnamamide derived from cinnamic acid **4b** delivered 6-membered dihydroquinolinone **5b**, instead of oxindole, in 25% yield (Scheme 2).



Scheme 2. Expansion of scope to a tetrahydroquinoline and a phenylcinnamamide derivative.

To further demonstrate the catalytic efficacy, we expanded the scope of this protocol to other isocyanide derivatives (Table 3). Various primary, secondary and tertiary aliphatic isocyanides were found compatible, furnishing the desired oxindoles in moderate to good yields (**3a**, **3t**-**3w**). Remarkably, tertiary aliphatic isocyanides showed better reactivity than primary or secondary isocyanides probably due to the effect of the stability of the corresponding carbon centered radicals. Moreover, the reaction showed good regio-selectivity in case

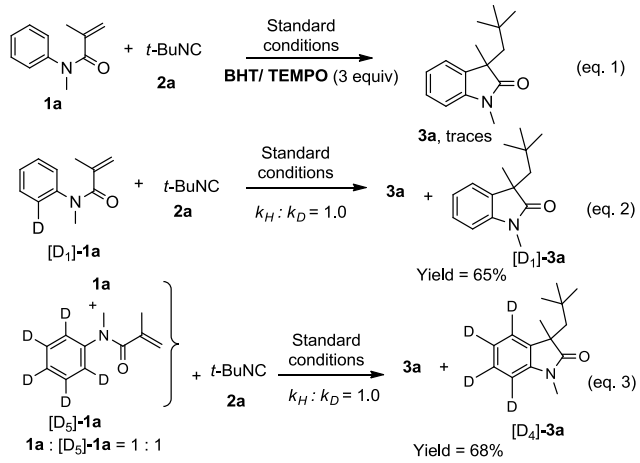
Table 3 Scope of isocyanides.[a, b]



[a] Reaction conditions: **1a** (0.2 mmol), **2** (5 equiv, 1 mmol), DCP (3 equiv), Cu_2O (15 mol%), EtOAc (2 mL) at 120 °C for 24 h. [b] Isolated yields. [c] 10 equiv of isocyanide used.

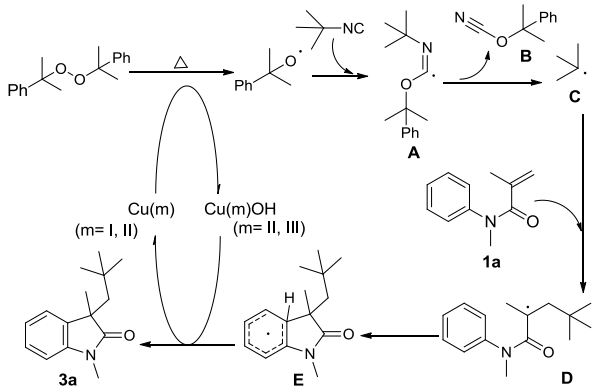
of linear isocyanide (**3w**). A moderate yield was obtained with bulky adamantyl isocyanide (**3x**) while a quite low yield was observed in case of benzylic isocyanide (**3y**). Also, ethyl 2-isocyanoacetate (**3z**) proved to be an effective substrate for the above reaction. However, the protocol failed to deliver the desired product in case of aromatic isocyanides.

To deduce the plausible reaction mechanism for this copper-catalyzed alkylation/cyclization of *N*-acrylamides with isocyanides, a series of control experiments were performed (Scheme 3). The presence of BHT or TEMPO hampered the reaction to a great extent, suggesting that a radical intermediate is involved in the catalytic cycle of the reaction (Scheme 3, eq. 1). Further, a series of deuteration reactions were carried out (Scheme 3, also see supporting information), where a kinetic isotope effect (KIE) of 1.0 was observed (Scheme 3, eq. 2 and 3).



Scheme 3 Control experiments and KIE studies.

On the basis of the above results and previous reports[4a,16] a plausible route has been proposed (Scheme 4). The first step involves the copper-assisted homolysis of DCP to generate the cumyloxyl radical.[9b,9e] Subsequently, attack of the cumyloxyl radical on the isonitrile generates another radical intermediate **A**, which is followed by homolytic cleavage affording **B** and *tert*-butyl radical **C**. Thereafter, addition of **C** to the C=C bond of *N*-acrylamide **1a** delivers **D.** The intramolecular cyclization of **D** followed by copper-assisted deprotonation generates the



Scheme 4 Plausible mechanism.

final product **3a** *via* intermediate **E.** As both Cu(I) and Cu(II) have catalytic activity for the reaction, with the former being more efficient, the oxidation state is designated with m ((m = I, II) to (m = II, III)) to include both.

Conclusions

We have developed a novel copper-catalyzed alkylarylation/cyclization cascade approach for the construction of alkyl substituted 3,3-disubstituted oxindoles *via* trapping of the alkyl radical generated from the isocyanide. The protocol shows remarkable regio-selectivity for the linear isocyanides and tolerates a series of functional groups, providing the desired products in moderate to high yields.

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